# Oral Contraceptives and Cancer Risk

Oral contraceptives (OCs) first became available to American women in the early 1960s. The convenience, effectiveness, and reversibility of action of birth control pills (which are popularly known as "the pill") has made them the most popular form of birth control in the United States. However, a correlation between estrogen and increased risk of breast cancer has led to continuing controversy about a possible link between OCs and cancer.

This fact sheet addresses only what is known about OC use and the risk of developing cancer. It does not deal with the most serious side effect of OC use—the increased risk of cardiovascular disease for certain groups of women.

## Oral Contraceptives

Currently, two types of OCs are available in the United States. The most commonly prescribed OC contains two synthetic versions of natural female hormones (estrogen and progesterone) that are similar to the hormones the ovaries normally produce. Estrogen stimulates the growth and development of the uterus at puberty, thickens the endometrium (the inner lining of the uterus) during the first half of the menstrual cycle, and stimulates changes in breast tissue at puberty and childbirth. Two types of synthetic estrogens are used in OCs, ethinyl estradiol and mestranol.

Progesterone, which is produced during the last half of the menstrual cycle, prepares the endometrium to receive the egg. If the egg is fertilized, progesterone secretion continues, preventing release of additional eggs from the ovaries. For this reason, progesterone is called the "pregnancy-supporting" hormone, and scientists believe it to have valuable contraceptive effects. The synthetic progesterone used in OCs is called progestogen or progestin. Norethindrone and levonorgestrel are examples of synthetic progesterones used in OCs.

The second type of OC available in the United States is called the minipill and contains only a progestogen. The minipill is less effective in preventing pregnancy than the combination pill, so it is prescribed less often.

Because medical research suggests that cancers of the female reproductive organs sometimes depend on naturally occurring sex hormones for their development and growth, scientists have been investigating a possible link between OC use and cancer risk. Medical researchers have focused a great deal of attention on OC users over the past 30 years. This scrutiny has produced a wealth of data on OC use and the development of certain cancers, although results of these studies have not always been consistent.

**Breast Cancer**

A woman's risk of developing breast cancer depends on several factors, some of which are related to her natural hormones. Hormonal factors that increase the risk of breast cancer include conditions that allow high levels of estrogen to persist for long periods of time, such as early age at first menstruation (before age 12), late age at menopause (after age 55), having children after age 30, and not having children at all. A woman’s risk of breast cancer increases with the amount of time she is exposed to estrogen.

Because many of the risk factors for breast cancer are related to natural hormones, and because OCs work by manipulating these hormones, there has been some concern about the possible effects of medicines such as OCs on breast cancer risk, especially if women take them for many years. Sufficient time has elapsed since the introduction of OCs to allow investigators to study large numbers of women who took birth control pills for many years beginning at a young age and to follow them as they became older.

However, studies examining the use of OCs as a risk factor for breast cancer have produced inconsistent results. Most studies have not found an overall increased risk for breast cancer associated with OC use. In June 1995, however, investigators at the National Cancer Institute (NCI) reported an increased risk of developing breast cancer among women under age 35 who had used birth control pills for at least 6 months, compared with those who had never used OCs. They also saw a slightly lower, but still elevated, risk among women ages 35 to 44. In addition, their research showed a higher risk among long-term OC users, especially those who had started to take the pill before age 18.

A 1996 analysis of worldwide epidemiologic data, which included information from the 1995 study, found that women who were current or recent users of birth control pills had a slightly elevated risk of developing breast cancer. However, 10 years or more after they stopped using OCs, their risk of developing breast cancer returned to the same level as if they had never used birth control pills.

To conduct this analysis, the researchers examined the results of 54 studies conducted in 25 countries that involved 53,297 women with breast cancer and 100,239 women without breast cancer. More than 200 researchers participated in this combined exhaustive analysis of their original studies, which represented about 90 percent of the epidemiological studies throughout the world that had investigated the possible relationship between OCs and breast cancer.

The return of risk to normal levels after 10 years or more of not taking OCs was consistent regardless of family history of breast cancer, reproductive history, geographic area of residence, ethnic background, differences in study designs, dose and type of hormone, and duration of use. The change in risk also generally held true for age at first use; however, for reasons that were not fully understood, there was a continued elevated risk among women who had started to use OCs before age 20.

One encouraging aspect of the study is that the slightly elevated risk seen in both current OC users and those who had stopped use less than 10 years previously may not be due to the contraceptive itself. The slightly elevated risk may result from the potential of estrogen to promote the growth of breast cancer cells that are already present, rather than its potential to initiate changes in normal cells leading to the development of cancer.

Furthermore, the observation that the slightly elevated risk of developing breast cancer that was seen in this study peaked during use, declined gradually after OC use had stopped, then returned to normal risk levels 10 years or more after stopping, is not consistent with the usual process of carcinogenesis. It is more typical for cancer risk to peak decades after exposure, not immediately afterward. Cancer usually is more likely to occur with increased duration and/or degree of exposure to a carcinogen. In this analytical study, neither the dose and type of hormone nor the duration of use affected the risk of developing breast cancer.

**Ovarian and Endometrial Cancers**

Many studies have found that using OCs reduces a woman's risk of ovarian cancer by 40 to 50 percent compared with women who have not used OCs. The Centers for Disease Control and Prevention's (CDC) Cancer and Steroid Hormone Study (CASH), along with other research conducted over the past 20 years, shows that the longer a woman uses OCs, the lower

her risk of ovarian cancer. Moreover, this lowered risk persists long after OC use ceases. The CASH study found that the reduced risk of ovarian cancer is seen in women who have used OCs for as little as 3 to 6 months, and that it continues for 15 years after use ends. Other studies have confirmed that the reduced risk of ovarian cancer continues for at least 10 to 15 years after a woman has stopped taking OCs. Several hypotheses have been offered to explain how oral contraceptives might protect against ovarian cancer, such as a reduction in the number of ovulations a woman has during her lifetime, but the exact mechanism is still not known.

Researchers have also found that OC use may reduce the risk of endometrial cancer. Findings from the CASH study and other reports show that combination OC use can protect against the development of endometrial cancer. The CASH study found that using combination OCs for at least 1 year reduced the risk of developing endometrial cancer to half of that seen for women who never took birth control pills. In addition, the beneficial effect of OC use persisted for at least 15 years after OC users stopped taking birth control pills. Some researchers have found that the protective effect of OCs against endometrial cancer increases with the length of time combination OCs are used, but results have not been consistent.

The reduction in risk of ovarian and endometrial cancers from OC use does not apply to the sequential type of pill, in which each monthly cycle contains 16 estrogen pills followed by 5 estrogen-plus-progesterone pills. (Sequential OCs were taken off the market in 1976, so few women have been exposed to them.) Researchers believe OCs reduce cancer risk only when the estrogen content of birth control pills is balanced by progestogen in the same pill.

**Cancer of the Cervix**

There is some evidence that long-term use of OCs may increase the risk of cancer of the cervix (the narrow, lower portion of the uterus). The results of studies conducted by NCI

scientists and other researchers support a relationship between extended use of the pill (5 or more years) and a slightly increased risk of cervical cancer. However, the exact nature of the association between OC use and risk of cervical cancer remains unclear.

One reason that the association is unclear is that two of the major risk factors for cervical cancer (early age at first intercourse and a history of multiple sex partners) are related to sexual behavior. Because these risk factors may be different between women who use OCs and those who have never used them, it is difficult for researchers to determine the exact role that OCs may play in the development of cervical cancer.

Also, many studies on OCs and cervical cancer have not accounted for the influence of human papillomaviruses (HPVs) on cervical cancer risk. HPVs are a group of more than 70 types of viruses, some of which are known to increase the risk of cervical cancer. Compared to non-OC users, women who use OCs may be less likely to use barrier methods of contraception (such as condoms). Since condoms can prevent the transmission of HPVs, OC users who do not use them may be at increased risk of becoming infected with HPVs. Therefore, the increased risk of cervical cancer that some studies found to be caused by prolonged OC use may actually be the result of HPV infection.

There is evidence that pill users who never use a barrier method of contraception or who have a history of genital infections are at a higher risk for developing cervical cancer. This association supports the theory that OCs may act together with sexually transmitted agents (such as HPVs) in the development of cervical cancer. Researchers continue to investigate the exact nature of the relationship between OC use and cancer of the cervix.

OC product labels have been revised to inform women of the possible risk of cervical cancer. The product labels also warn that birth control pills do not protect against human

immunodeficiency virus (HIV) and other sexually transmitted diseases such as HPV, chlamydia, and genital herpes.

**Liver Tumors**

There is some evidence that OCs may increase the risk of certain malignant (cancerous) liver tumors. However, the risk is difficult to evaluate because of different patterns of OC use and because these tumors are rare in American women (the incidence is approximately 2 cases per 100,000 women). A benign (noncancerous) tumor of the liver called hepatic adenoma has also been found to occur, although rarely, among OC users. These tumors do not spread, but they may rupture and cause internal bleeding.

**Reducing Risks**

After many years on the U.S. market, the overall health effects of OCs are still mixed. The most serious side effect of the pill continues to be an increased risk of cardiovascular disease in certain groups, such as women who smoke; women over age 35; obese women; and those with a history of high blood pressure, diabetes, or elevated serum cholesterol levels. More information about the increased risk of cardiovascular disease is available from the National Heart, Lung, and Blood Institute (NHLBI). The NHLBI Information Center can be reached at:

**Address:** Post Office Box 30105
Bethesda, MD 20824–0105
**Telephone:** 301–592–8573
**Fax:** 301–592–8563
**E-mail:** NHLBIinfo@rover.nhlbi.nih.gov
**Internet Web site:** http://www.nhlbi.nih.gov

The NCI recommends that women in their forties or older get screening mammograms on a regular basis, every 1 to 2 years. Women who are at increased risk for breast cancer should

seek medical advice about when to begin having mammograms and how often to be screened. A high-quality mammogram, with a clinical breast exam (an exam done by a professional health care provider), is the most effective way to detect breast cancer early.

Women who are or have been sexually active or are in their late teens or older can reduce their risk for cervical cancer by having regular Pap tests. Research has shown that women who have never had a Pap test or who have not had one for several years have a higher-than-average risk of developing cervical cancer.

Women who are concerned about their risk for cancer are encouraged to talk with their doctor. More information is also available from the Cancer Information Service (see below).

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## Sources of National Cancer Institute Information

**Cancer Information Service**

Toll-free: 1–800–4–CANCER (1–800–422–6237)
TTY (for deaf and hard of hearing callers): 1–800–332–8615

**NCI Online**

***Internet***

Use http://www.cancer.gov to reach NCI's Web site.

***CancerMail Service***

To obtain a contents list, send e-mail to cancermail@icicc.nci.nih.gov with the word "help" in the body of the message.

**CancerFax®** fax on demand service

Dial 301–402–5874 and listen to recorded instructions.

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